Precision medicine from the basic to translational science perspective

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Disclosures

- financial support for research from AbbVie, Biora Therapeutics, Landos, Pfizer, Sossei Heptares and Takeda.

- speaker‘s fees from Abbvie, Biogen, Bristol Myers Squibb, Celltrion, Chiesi, Falk, Ferring, Galapagos, Janssen, Lily, MSD, Pfizer, R-Biopharm, Takeda, Tillots Pharma, Truvion and Viatris.

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Precision medicine is universal

*"Doctors have always recognized that **every patient is unique**, and doctors have always tried to **tailor their treatments** as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. **What if matching a cancer cure to our genetic code was just as easy**, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"*

President Obama, January 30, 2015
State of the Union

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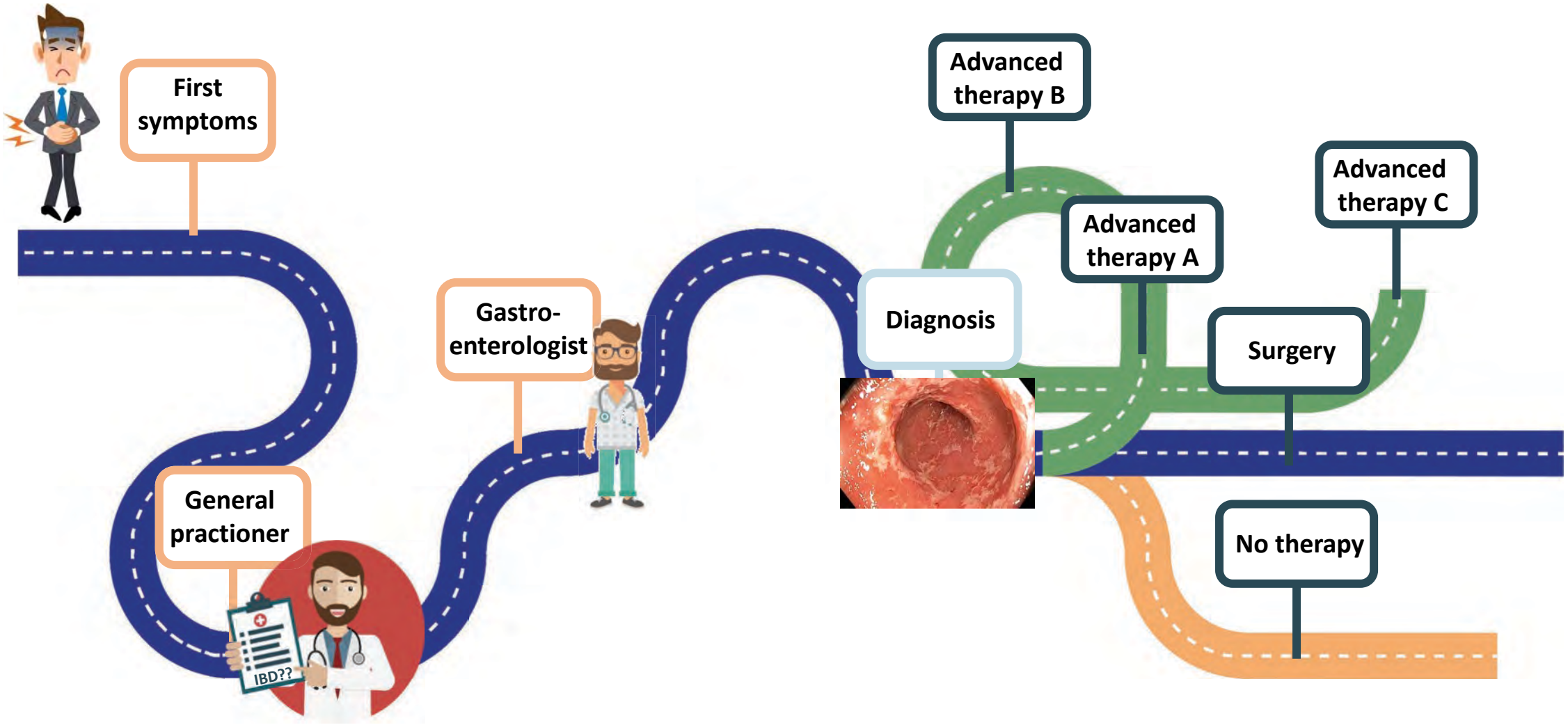
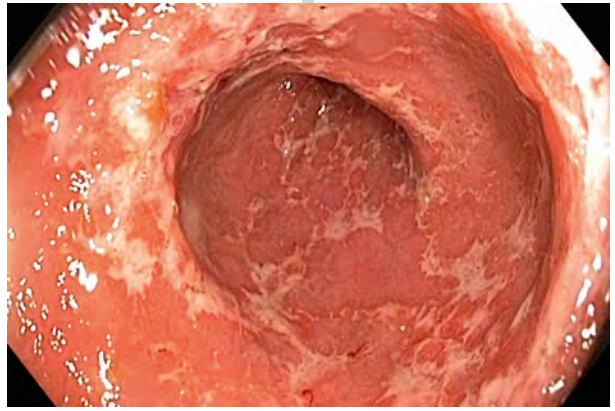
Precision medicine in IBD

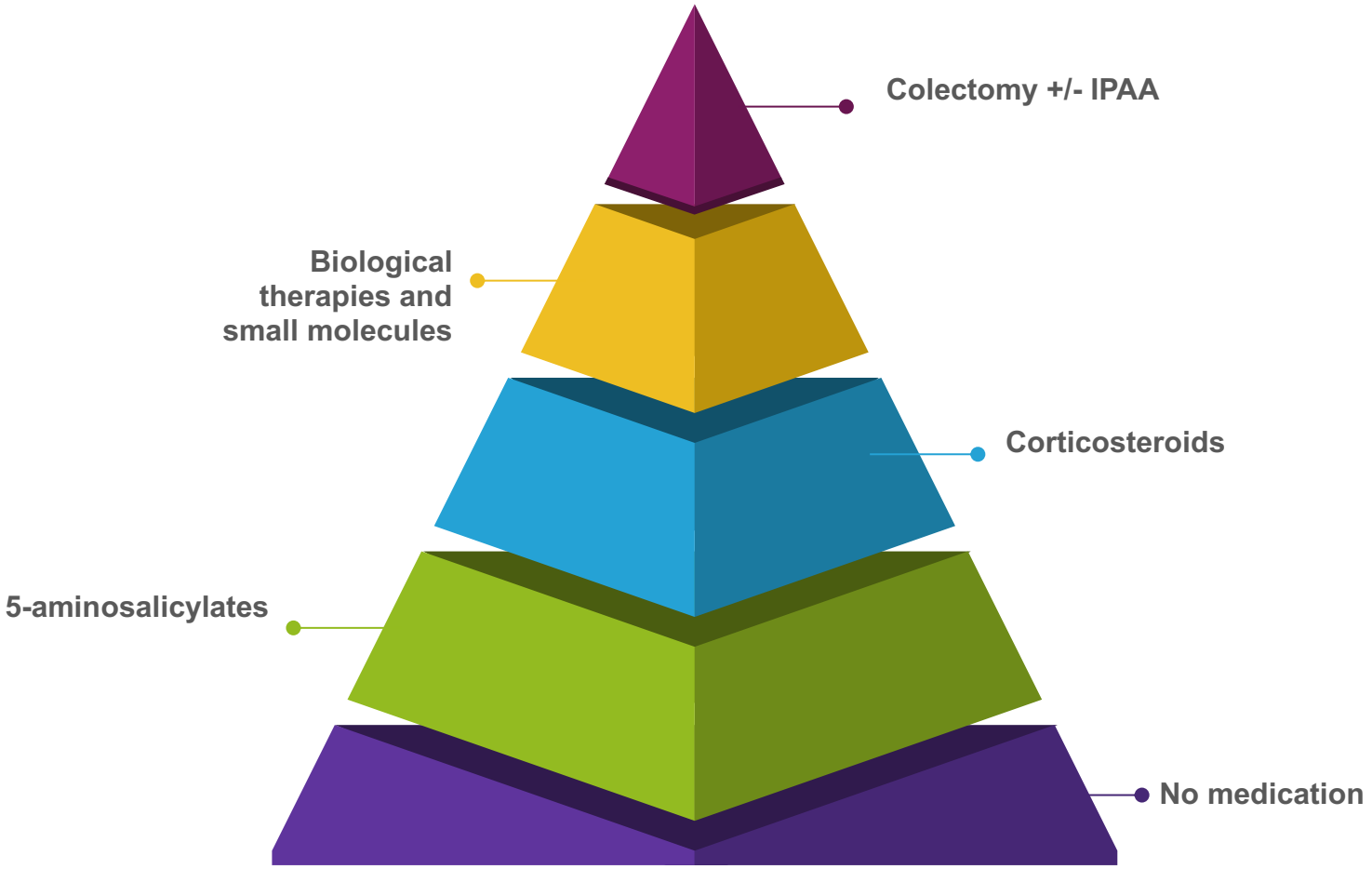


Courtesy Sare Verstockt

Precision medicine in IBD

Diagnosis





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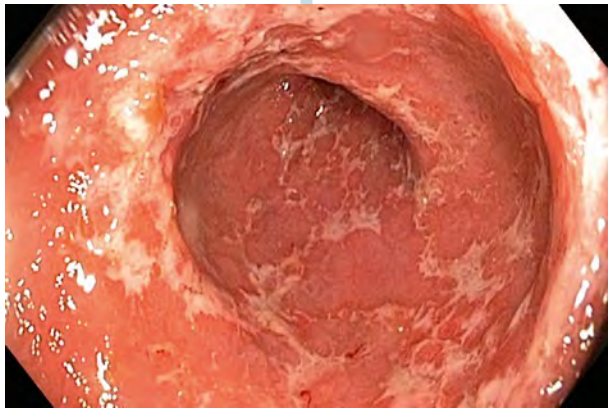
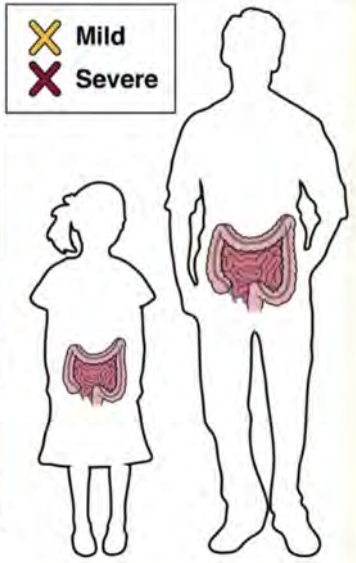
Precision medicine in IBD

Diagnosis



Disease severity variables	CD	UC
Clinical		
Limited anatomic extent	X	X
Growth impairment (pediatric)	X	
Age at diagnosis <14 years	X	X
Age at diagnosis <40 years (adults)	X	X
Smoking history	X	
Perianal or severe rectal disease	X	
Penetrating disease	X	
Stricturing disease	X	
Multi- or long-segment ileal (>20 cm), disease proximal to TI	X	
Extensive bowel involvement	X	X
Emergent diagnosis, hospitalization	X	X
Delay in diagnosis	X	X
Need for systemic steroids	X	X
C difficile, cytomegalovirus infection		X
Serologies		
ASCA (+)	X	
ANCA (+)	X	X
Anti-Cbir (+) (UC: pediatric)	X	X
Anti-GMCSF (+)	X	
Genetic		
NOD2 mutation	X	

Disease activity variables*
Clinical
Symptoms
Biomarkers
C-reactive protein
Fecal calprotectin
Albumin
Hemoglobin
Endoscopic
Disease activity scores



* Based on data from Torres et al, Lancet, 2017 (CD) and Rubin et al, AJG, 2019 (UC)

Verstockt B et al. Gastroenterology 2022.
Agrawal et al. Gastroenterology 2021.

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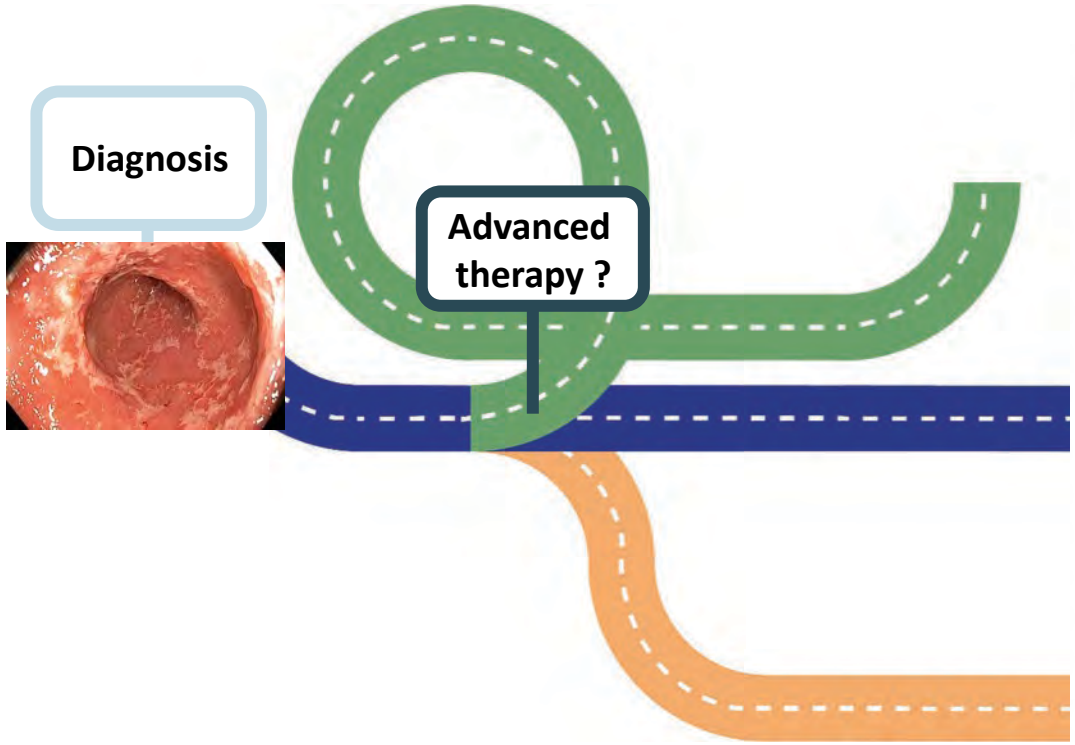
Precision medicine in IBD



Therapeutic arm	Placebo arm				
27.0 %	7.4 %	▲	19.6%	Etrasimod	ELEVATE UC 52
24.8 %	15.2 %	▲	9.6%	Etrasimod	ELEVATE UC 12
18.4 %	6.0 %	▲	12.4%	Ozanimod	TRUE NORTH
33.5 %	4.1 %	▲	29.4%	Upadacatinib	U-ACCOMPLISH
26.1 %	4.8 %	▲	21.3%	Upadacitinib	U-ACHIEVE
11.5 %	4.2 %	▲	7.3%	Filgotinib	SELECTION B
26.1 %	15.3 %	▲	10.8%	Filgotinib	SELECTION A
16.6 %	3.6 %	▲	13%	Tofacitinib	OCTAVE 2
18.5 %	8.2 %	▲	10.3%	Tofacitinib	OCTAVE 1
24.2 %	13.3 %	▲	10.9%	Mirikizumab	LUCENT 1
15.5 %	5.3 %	▲	10.2%	Ustekinumab	UNIFI
16.9 %	5.4 %	▲	11.5%	Vedolizumab	GEMINI
17.8 %	6.4 %	▲	11.4%	Golimumab	PURSUIT
16.5%	9.3 %	▲	6.7%	Adalimumab	ULTRA 2
33.9 %	5.7 %	▲	28.2%	Infliximab	ACT 2
38.8 %	14.9 %	▲	23.9%	Infliximab	ACT 1

Adapted from: Alsoud et al. Lancet Gastroenterology and Hepatology. 2021.

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Key principles in (IBD) biomarker development

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Key principles in (IBD) biomarker development

Define clear, objective and clinically relevant outcomes

- IBD-related surgery
- Stricture development
- Abscess development
- Time to colectomy
- Need for advanced therapy
- Bowel damage

- Clinical remission
- Steroid-free remission
- Endoscopic remission
- Histological remission
- Transmural remission
- Reduced disability

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Verstockt B et al. JCC 2022.

Key principles in (IBD) biomarker development

Standardisation of metadata (definitions) across independent studies

Verstockt B et al. JCC 2022.

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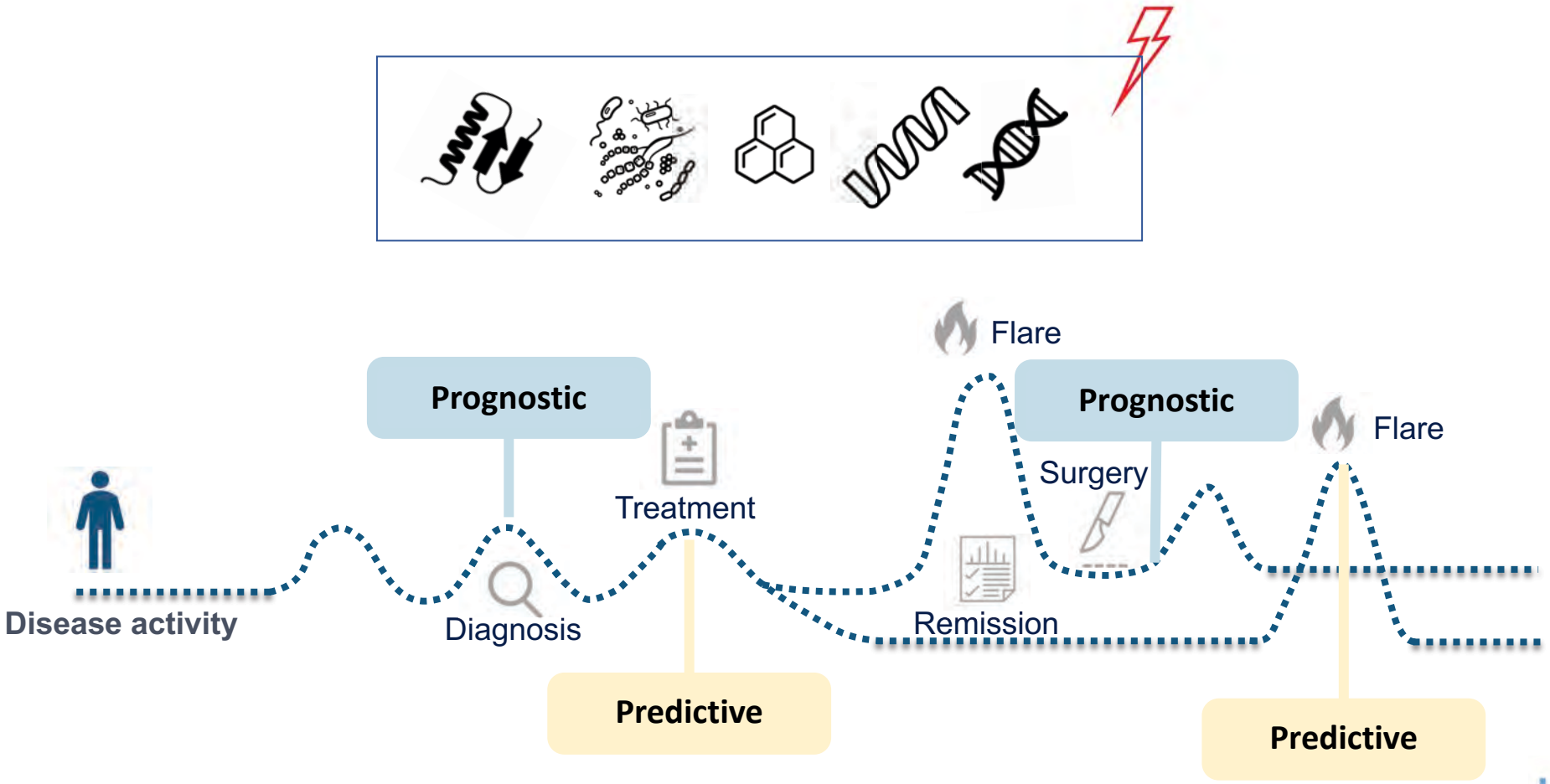
Key principles in (IBD) biomarker development

Assess biomarkers in specific patient populations and/or timepoints

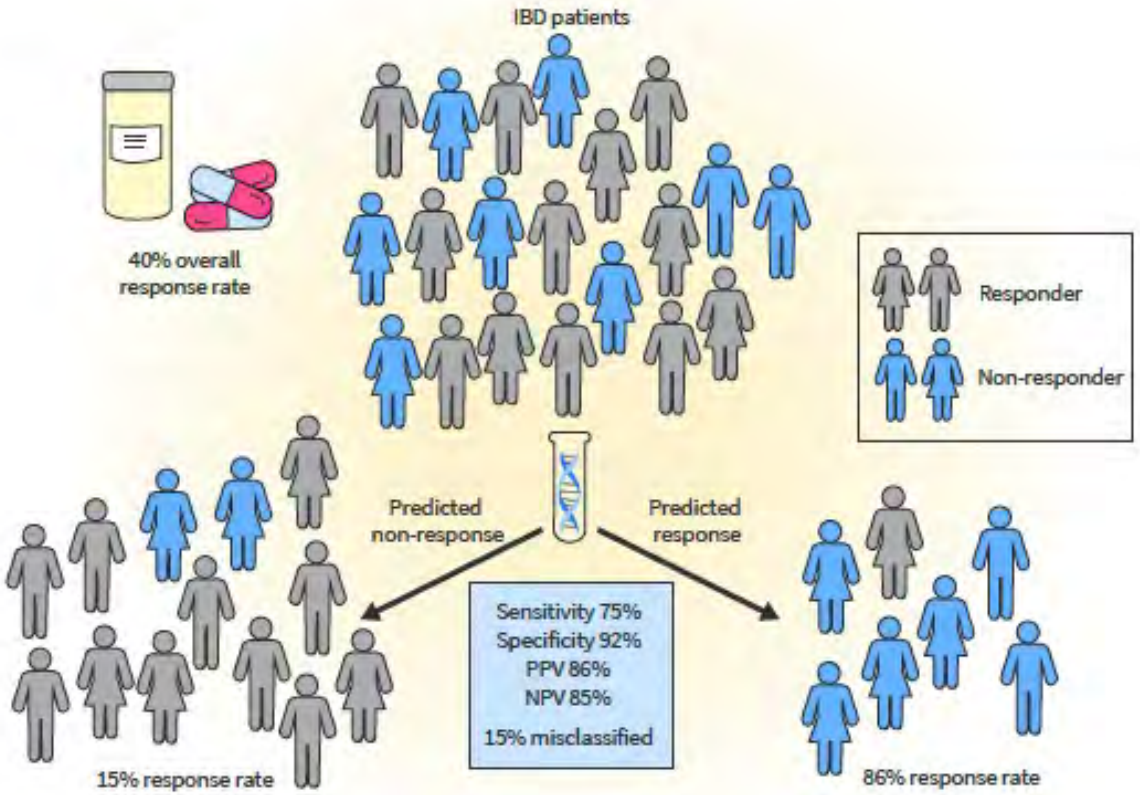


Adapted from : Verstockt B et al. JCC 2022.

Key principles in (IBD) biomarker development

Define criteria for evaluating performance and impact of new biomarkers

Communicate about uncertainty



Verstockt B et al. JCC 2022.
Verstockt B et al. Gastroenterology 2022.
Palmer-Jones et al. UEG Education 2023.

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How to move forward based on earlier experiences ?

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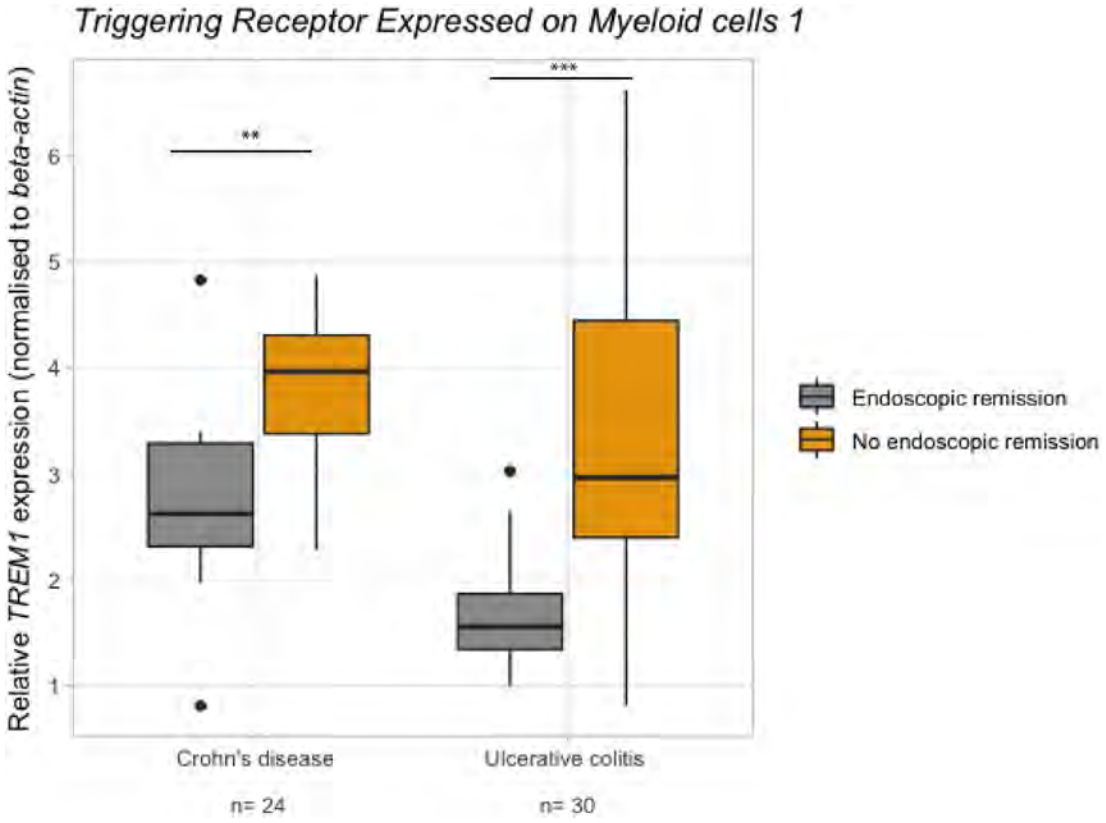
The path forward: embracing disease complexity



Amsterdam UMC
Universitair Medische Centra

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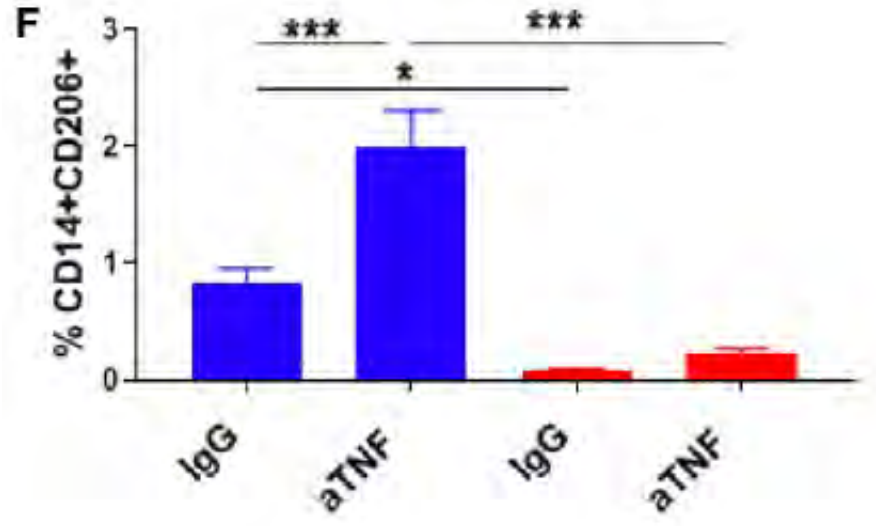

TREM1 low
TREM1 high

Gaujoux et al. Gut. 2018.
Verstockt B et al. Gut 2018.
Verstockt B et al. EbioMedicine 2019.
Prins et al. Frontiers in Immunology 2021.

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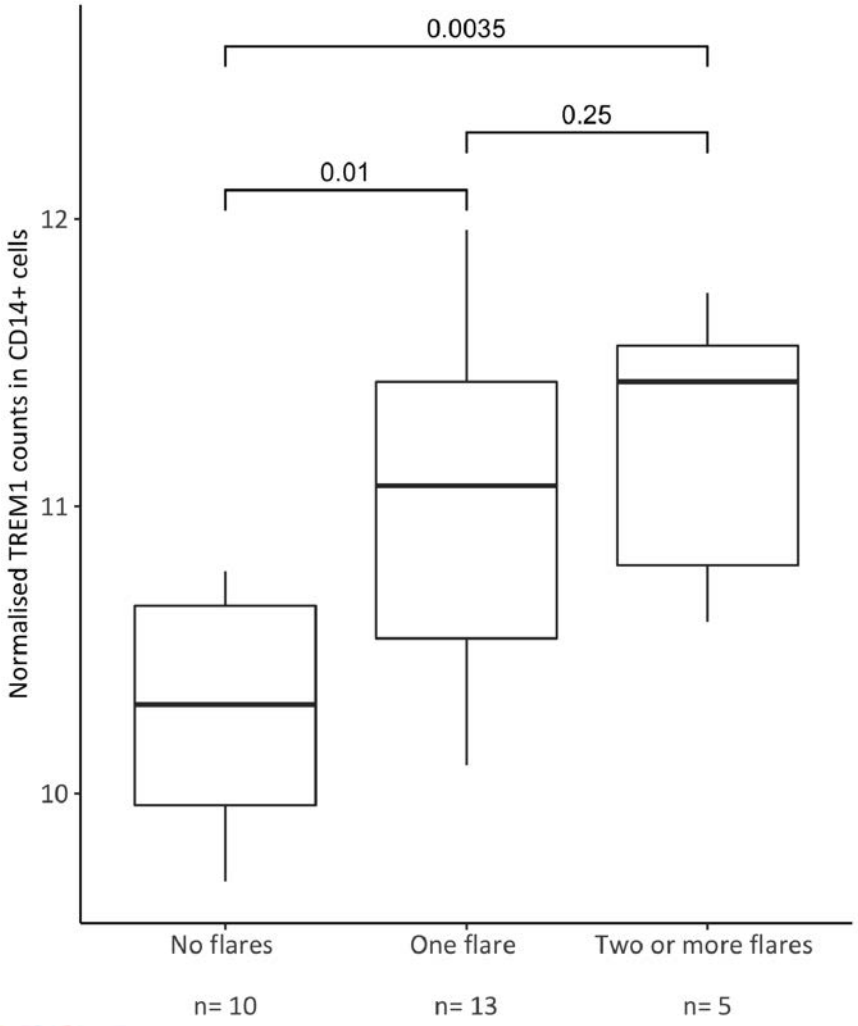
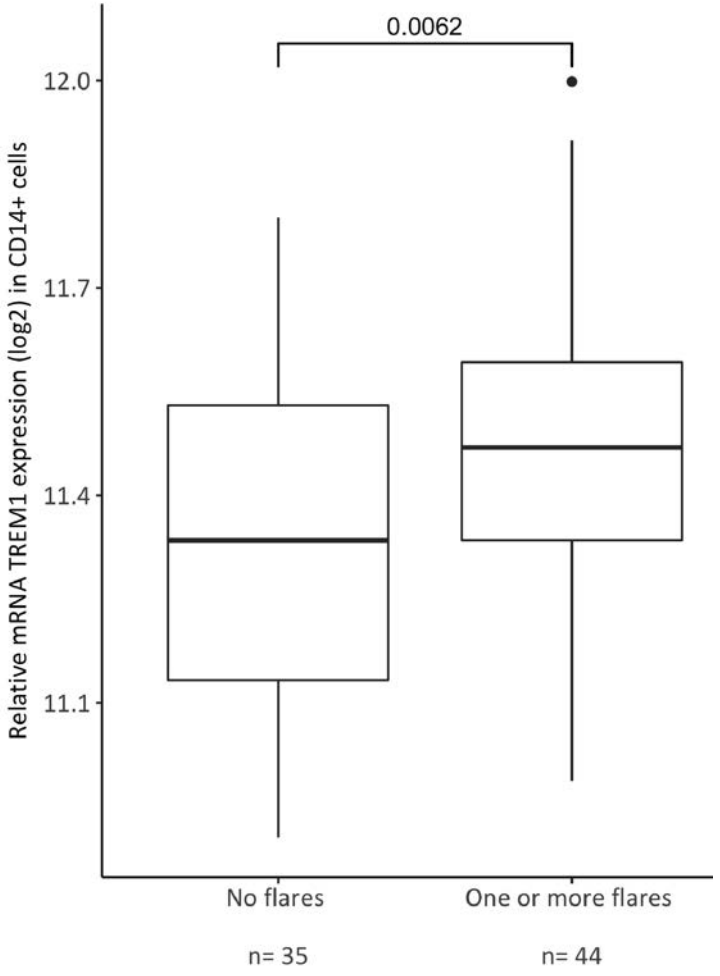
The path forward: embracing disease complexity

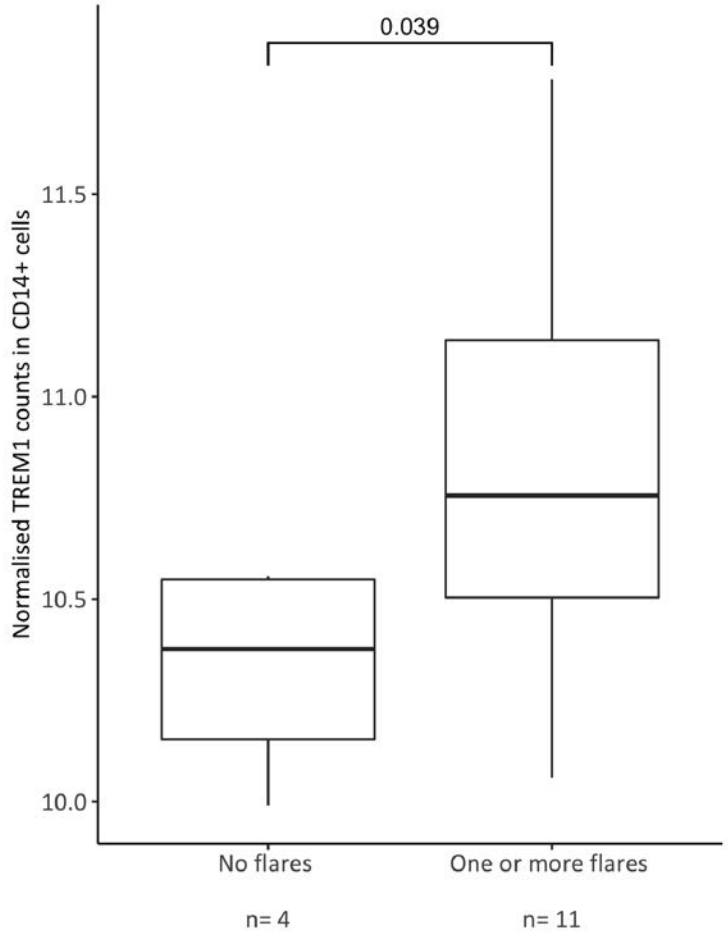


Discovery cohort



Validation 1 – Historic microarray cohort

Lee et al. JCI. 2011.



Validation 2 – New RNA seq cohort

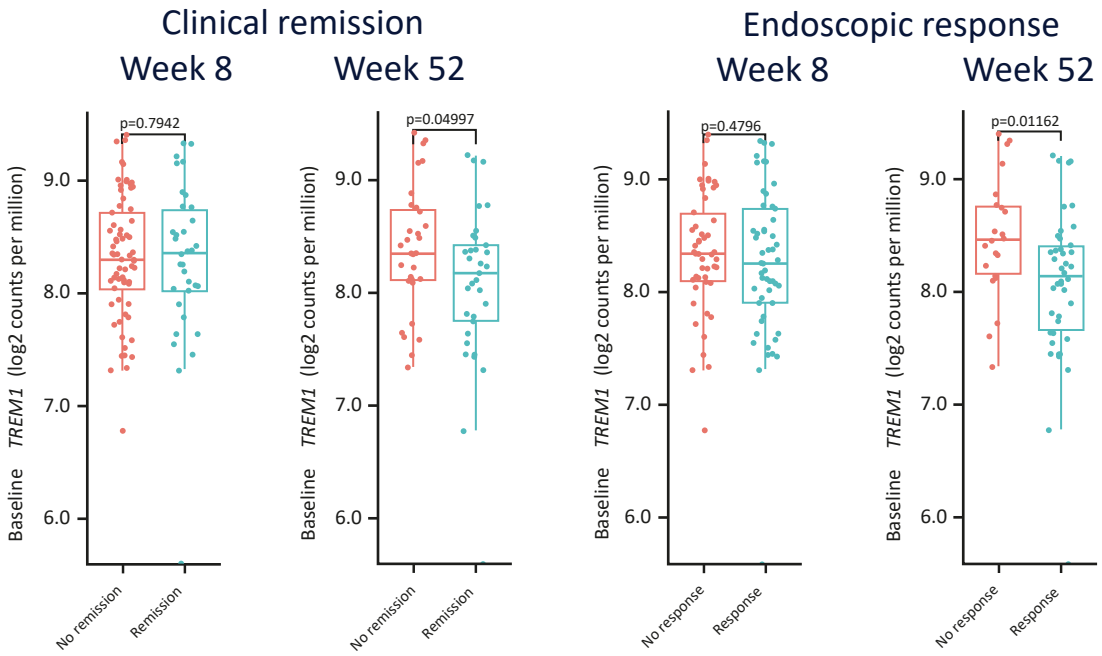
Verstockt B, Lee JCL. *Unpublished.*

UNIVERSITY OF CAMBRIDGE

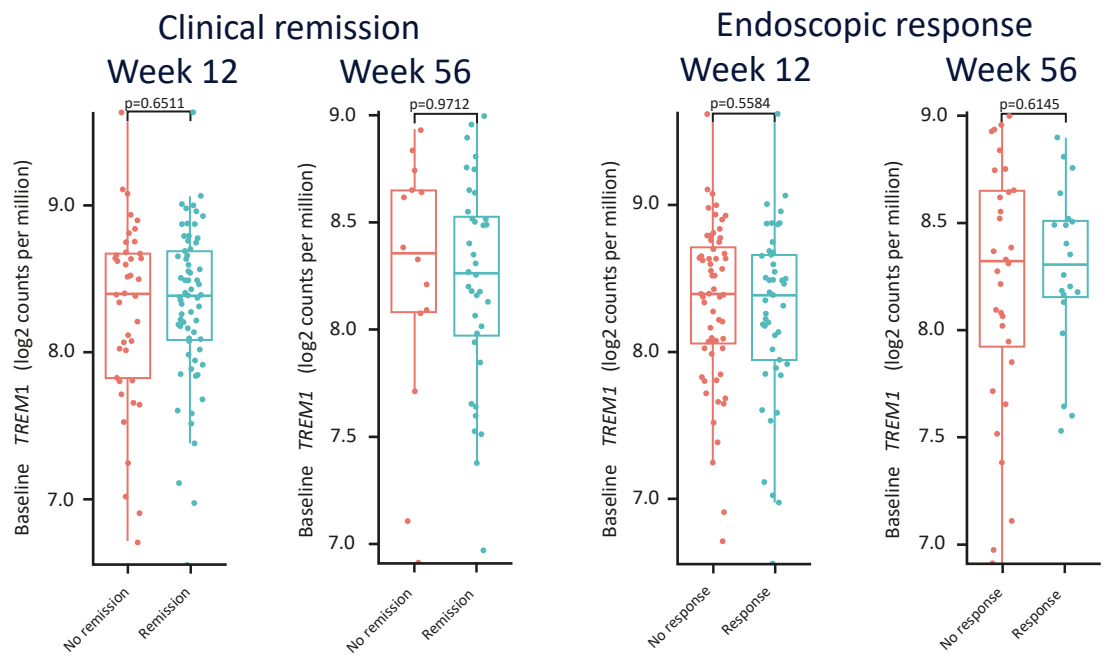
The path forward: embracing disease complexity

A single gene or protein is too simple for a complex disease like IBD

SERENE-UC



SERENE-CD



- *TREM1* was not linked to clinical response or endoscopic remission in SERENE-UC and SERENE-CD
- *TREM1* was not found to be predictive of clinical outcomes when stratified by drug levels in both studies

Verstockt B et al. JCC 2023.

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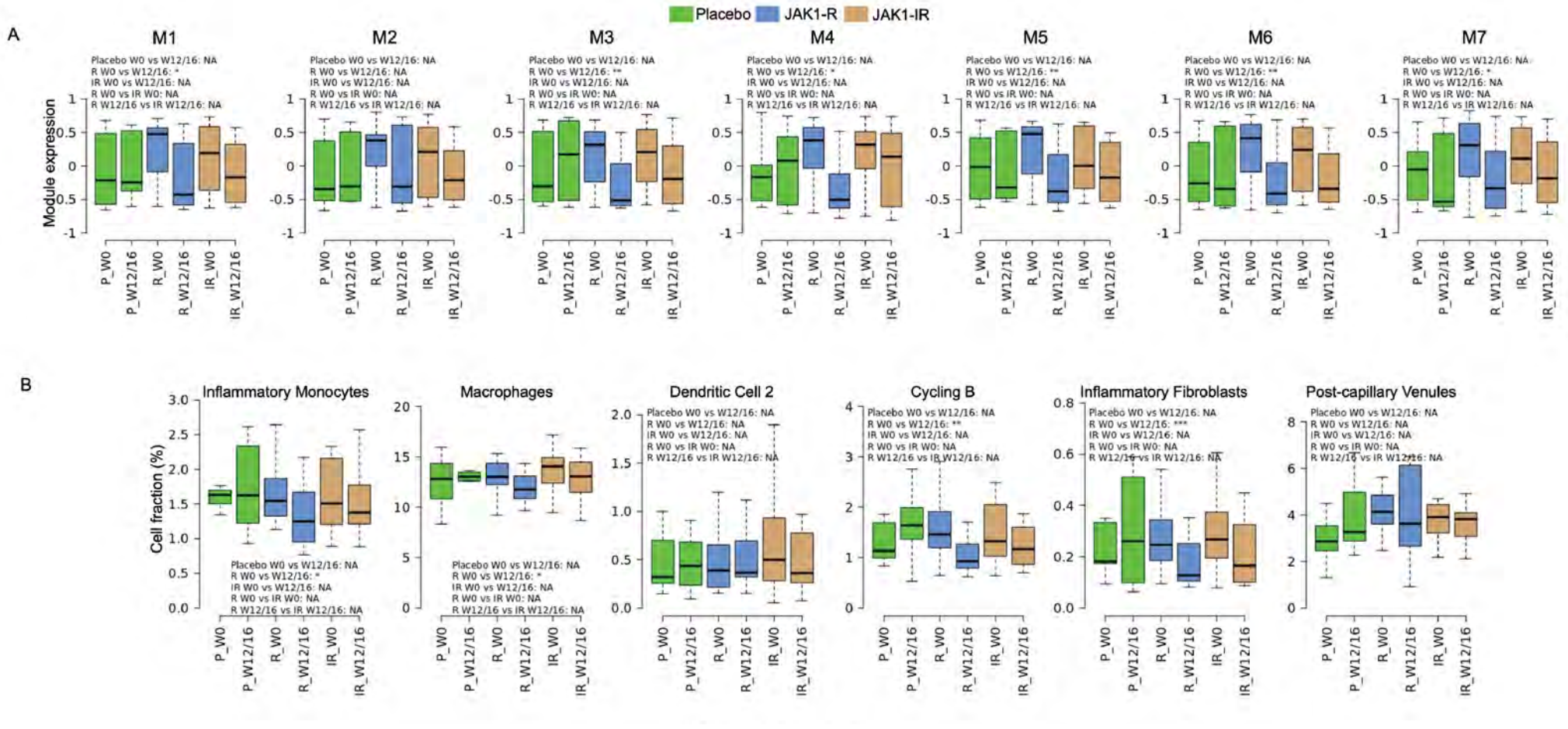
The path forward: embracing novel technologies



Smillie et al. Cell 2019.
Steere et al. Clinical and Translational Gastroenterology 2023.
Wang et al. IBD 2023.

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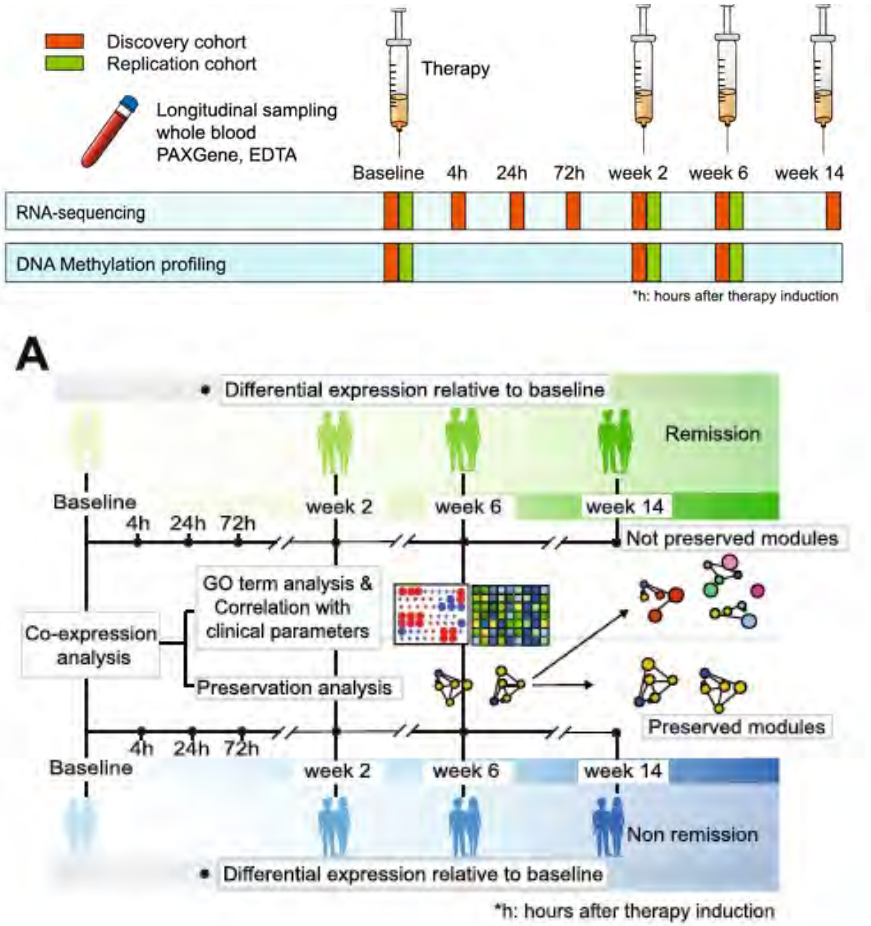
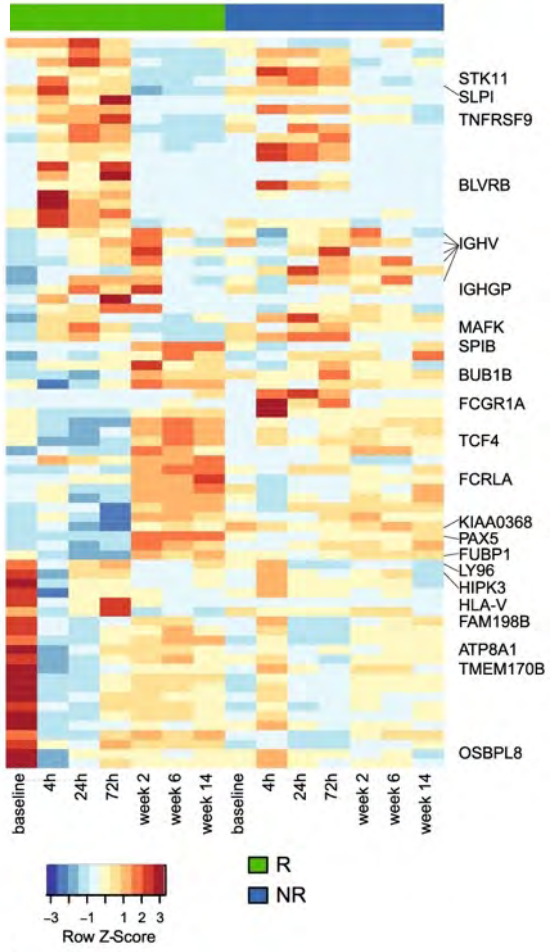
The path forward: look into dynamics of response





Mishra et al. Genome Medicine 2022.

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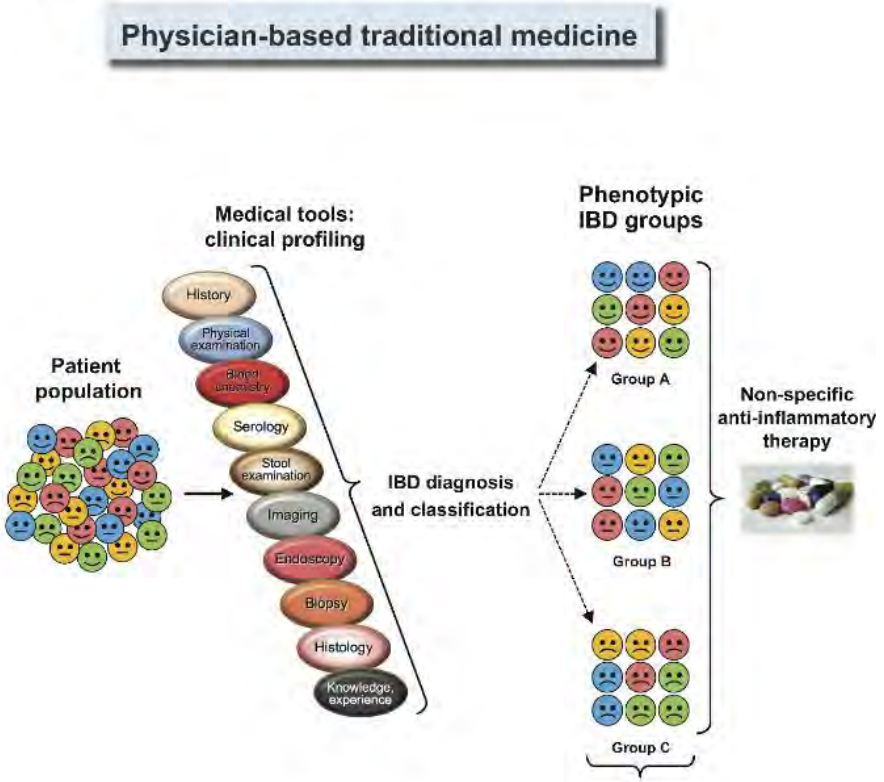
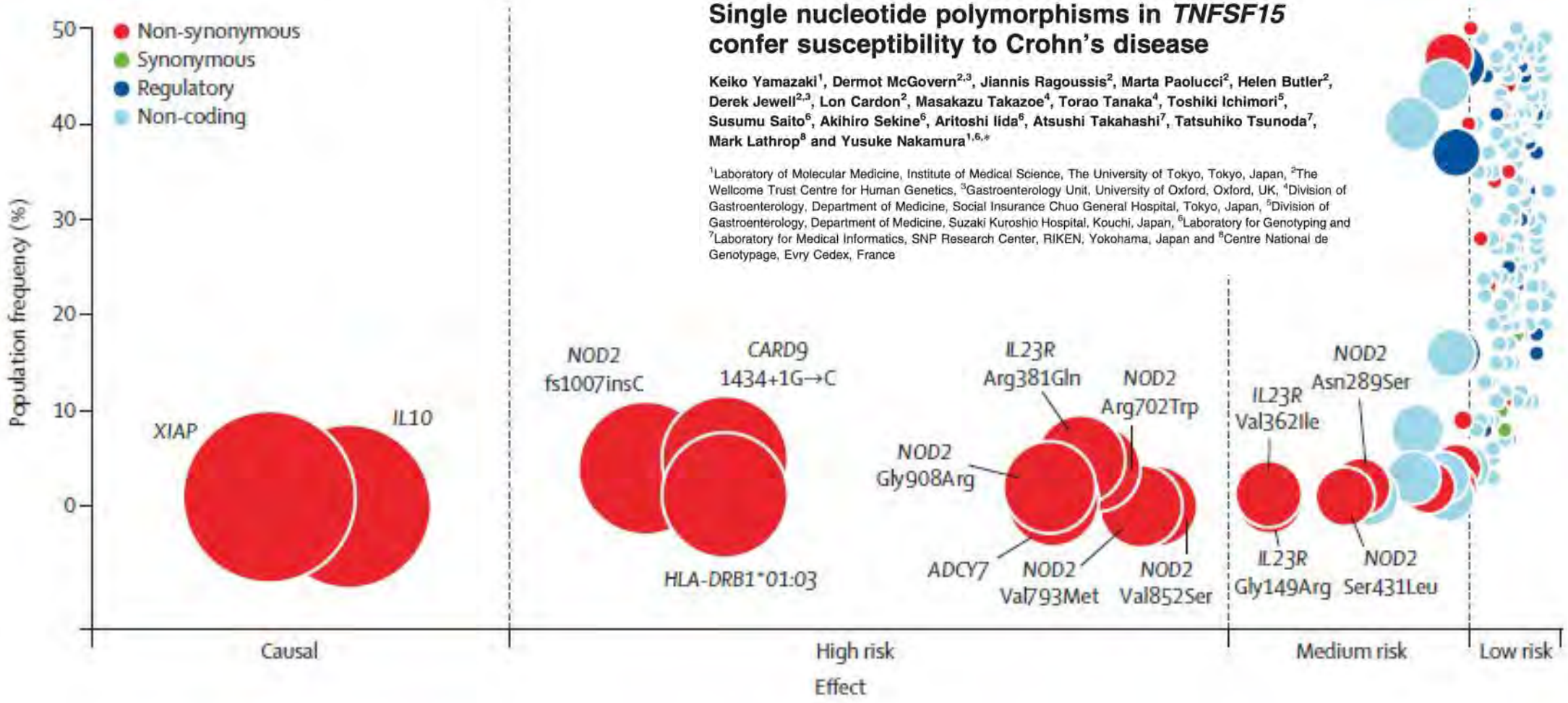
The path forward: reverting the process



Fiocchi et al. JCC 2022.

From the bed to the bench, the example of anti-TL1A therapy



Single nucleotide polymorphisms in *TNFSF15* confer susceptibility to Crohn's disease

Keiko Yamazaki[1], Dermot McGovern[2,3], Jiannis Ragoussis[2], Marta Paolucci[2], Helen Butler[2], Derek Jewell[2,3], Lon Cardon[2], Masakazu Takazoe[4], Torao Tanaka[4], Toshiki Ichimori[5], Susumu Saito[6], Akihiro Sekine[6], Aritoshi Iida[6], Atsushi Takahashi[7], Tatsuhiko Tsunoda[7], Mark Lathrop[8] and Yusuke Nakamura[1,6,*]

[1]Laboratory of Molecular Medicine, Institute of Medical Science, The University of Tokyo, Tokyo, Japan, [2]The Wellcome Trust Centre for Human Genetics, [3]Gastroenterology Unit, University of Oxford, Oxford, UK, [4]Division of Gastroenterology, Department of Medicine, Social Insurance Chuo General Hospital, Tokyo, Japan, [5]Division of Gastroenterology, Department of Medicine, Suzaki Kuroshio Hospital, Kouchi, Japan, [6]Laboratory for Genotyping and [7]Laboratory for Medical Informatics, SNP Research Center, RIKEN, Yokohama, Japan and [8]Centre National de Genotypage, Evry Cedex, France

M Mirkov et al. Lancet Gastroenterol & Hepatol March 2017

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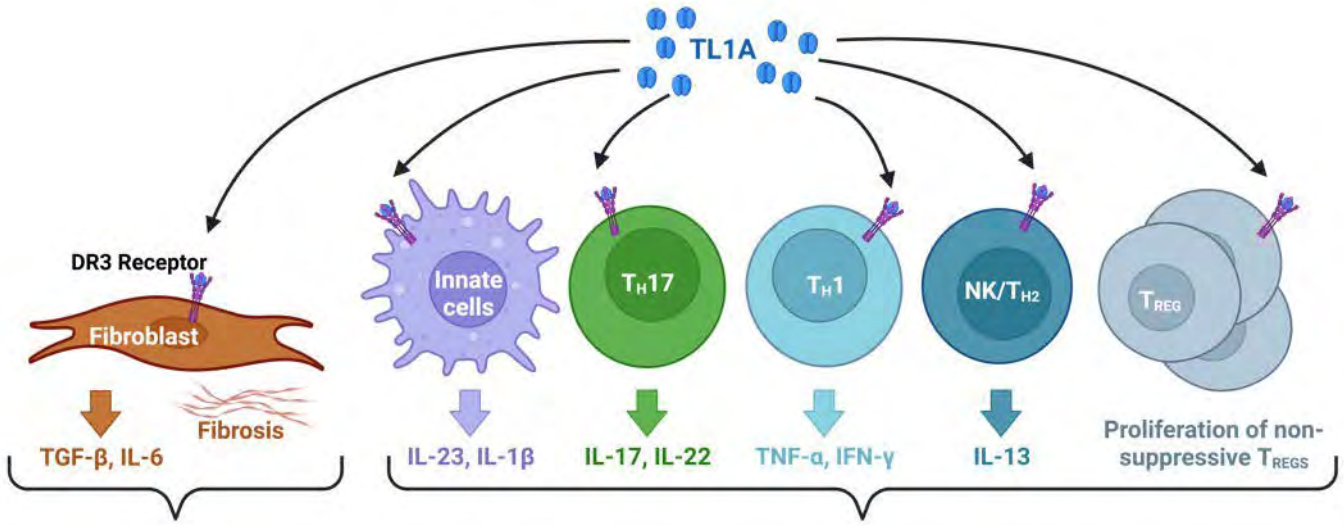
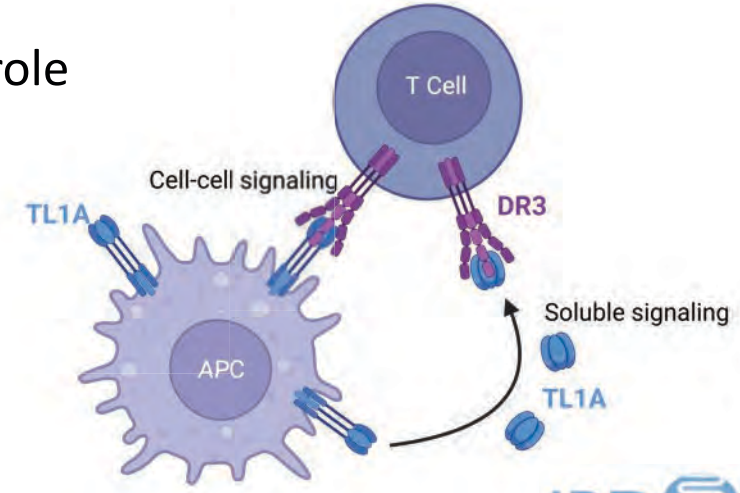
The example of anti-TL1A therapy



Proinflammatory and profibrotic role



Sands et al. UEGW 2023; Yu et al. J Biol Chem 1999; Jin et al. Mucosal Immunology 2013; Xu et al. Front Immunol 2022; Siakavellas et al. IBD 2015; Barett et al. Am J Pathol 2012; Takedatsu et al. Gastroenterology 2009; Jostins et al. 2012; Michelsen et al. Plos One 2009.

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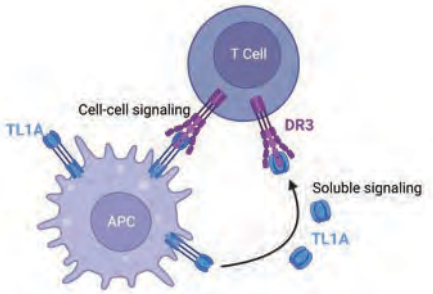
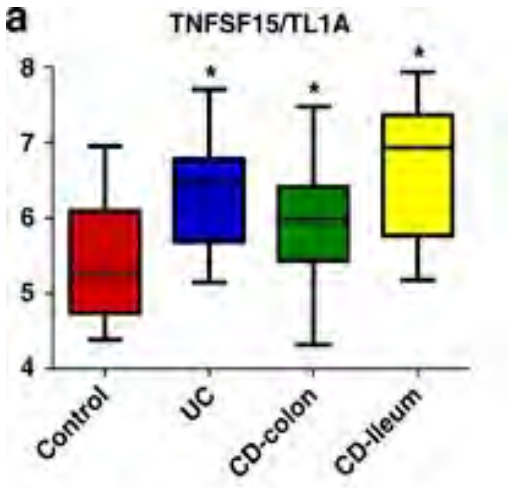
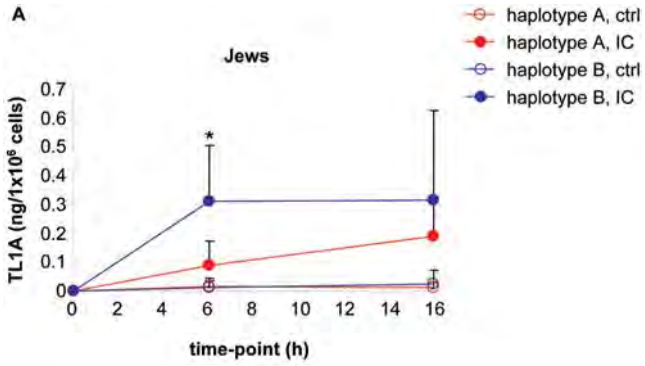
The example of anti-TL1A therapy

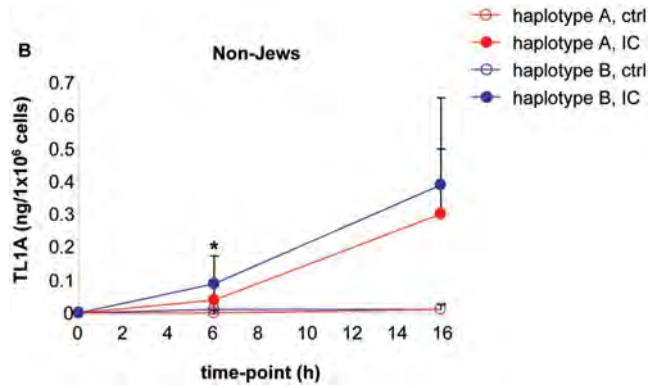


Tissue



Circulating monocytes





Allele associated with **risk for IBD** at ***TNFSF15*** might **increase its expression** and thereby **promote inflammation**

Population studied, the **disease status** of the subjects, the **cell type considered** and the **observed direction** of **effect differ between studies**, leaving the **mechanism** by which this **genetic locus confers susceptibility** to **IBD unclear**.

Jin et al. Mucosal Immunology 2013.

Michelsen et al. Plos One 2009.

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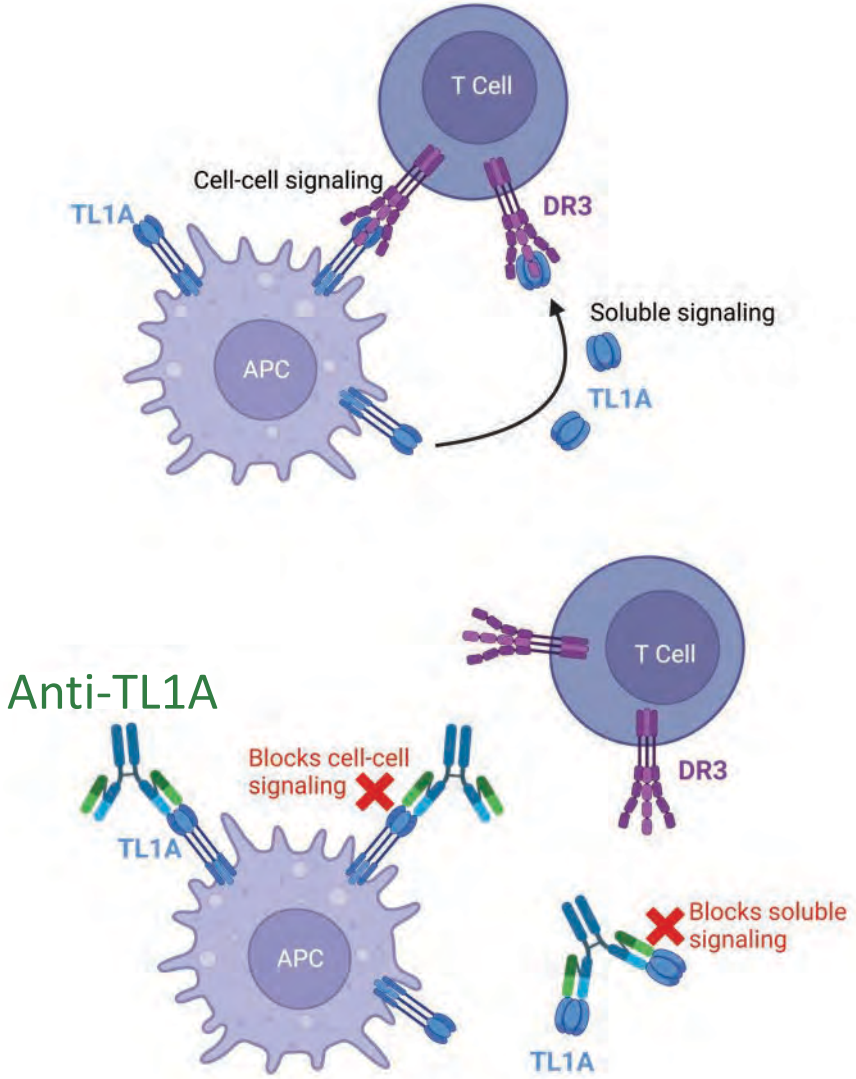
The example of anti-TL1A therapy



Sands et al. UEGW 2023; Danese et al. UEGW 2023.

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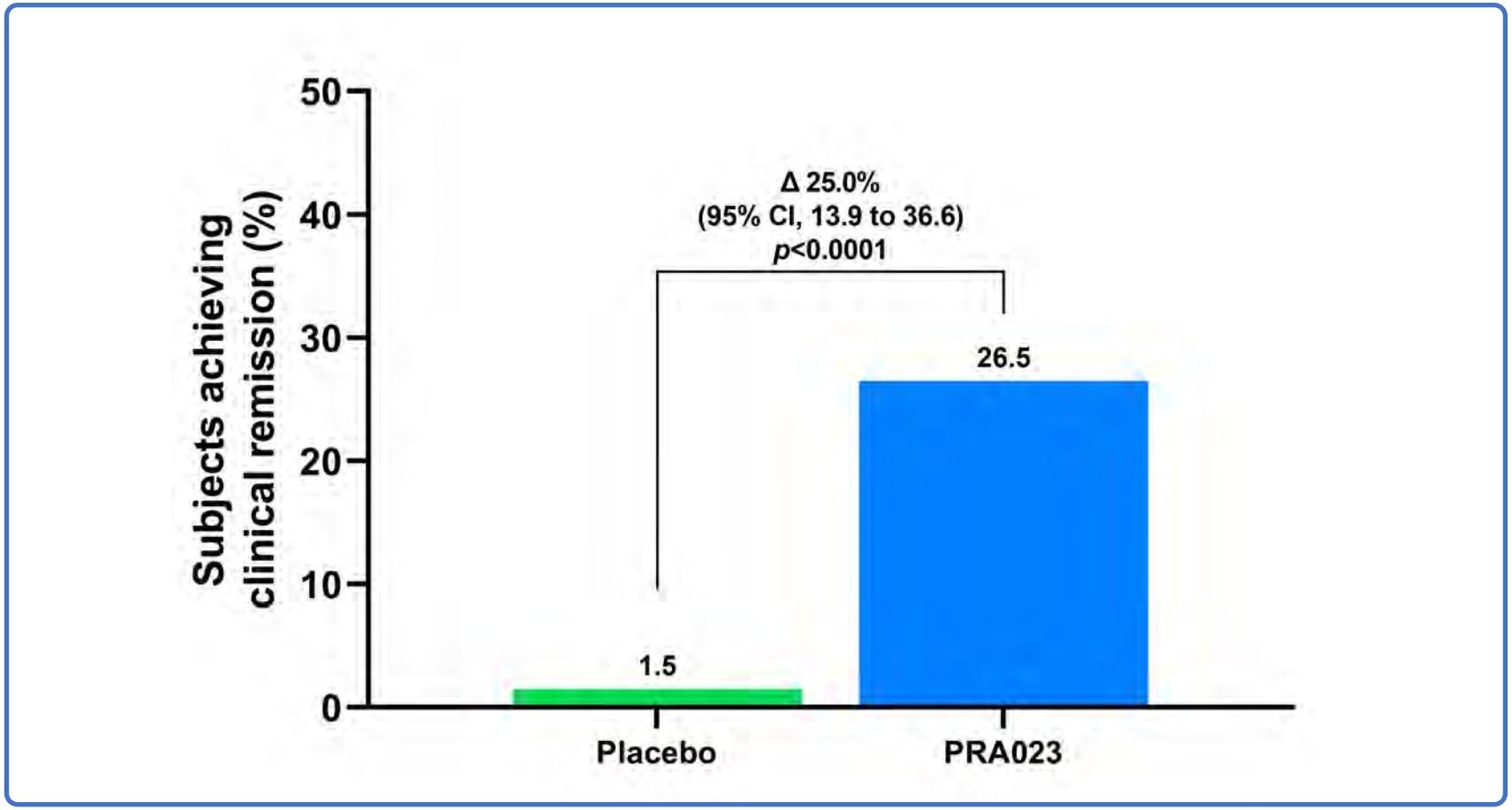
The example of anti-TL1A therapy



Clinical remission per modified Mayo score (mMS) is defined as endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or 1 and not greater than Baseline.

Sands et al. UEGW 2023.

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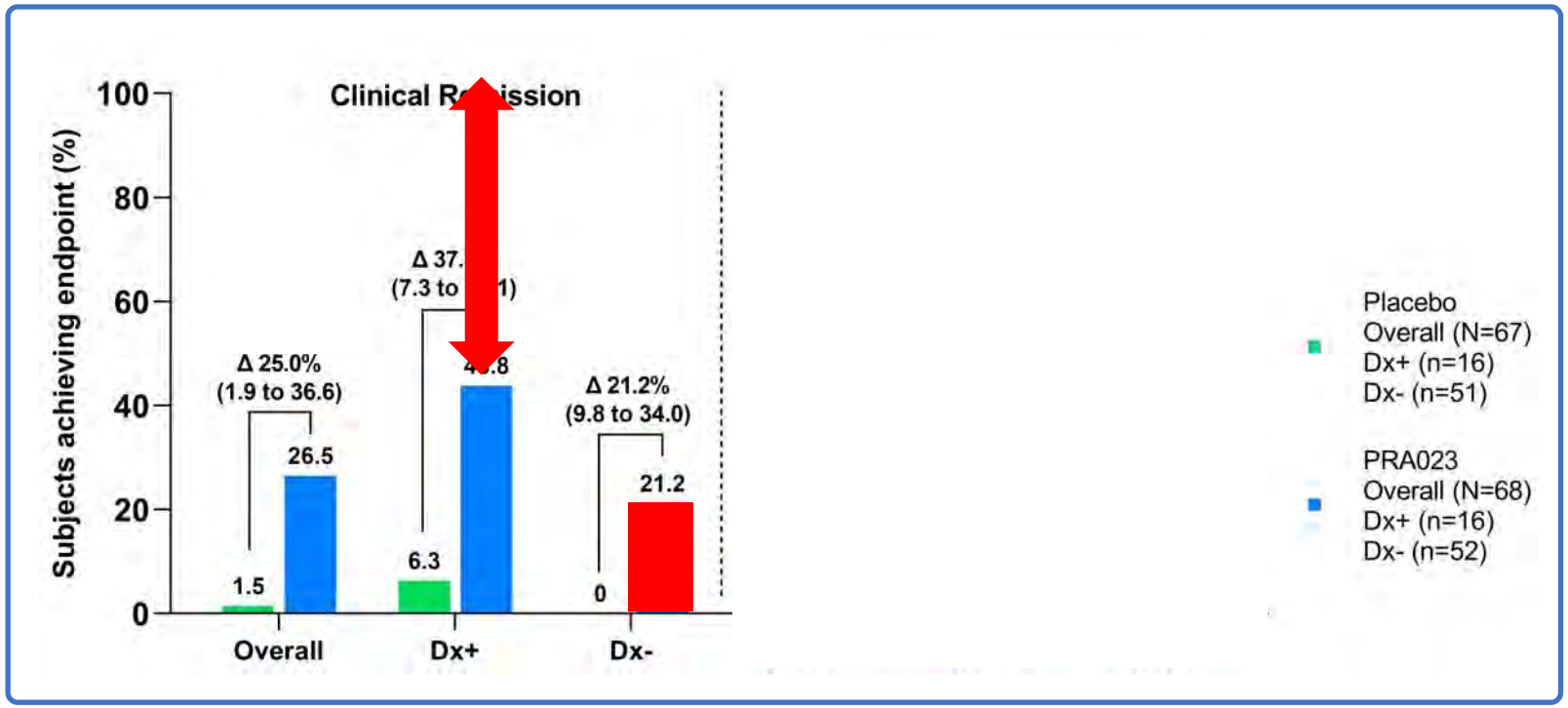
The example of anti-TL1A therapy



Clinical remission per mMs is defined as endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or 1 and not greater than baseline. Endoscopic improvement is defined as endoscopy subscore ≤1 with no friability. Numbers in parentheses are 95% confidence intervals.

Sands et al. UEGW 2023.

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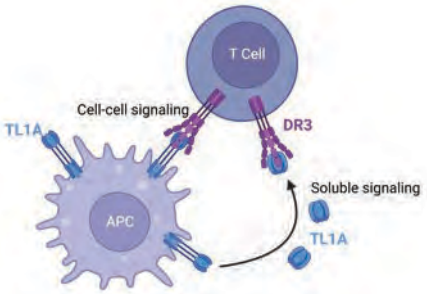
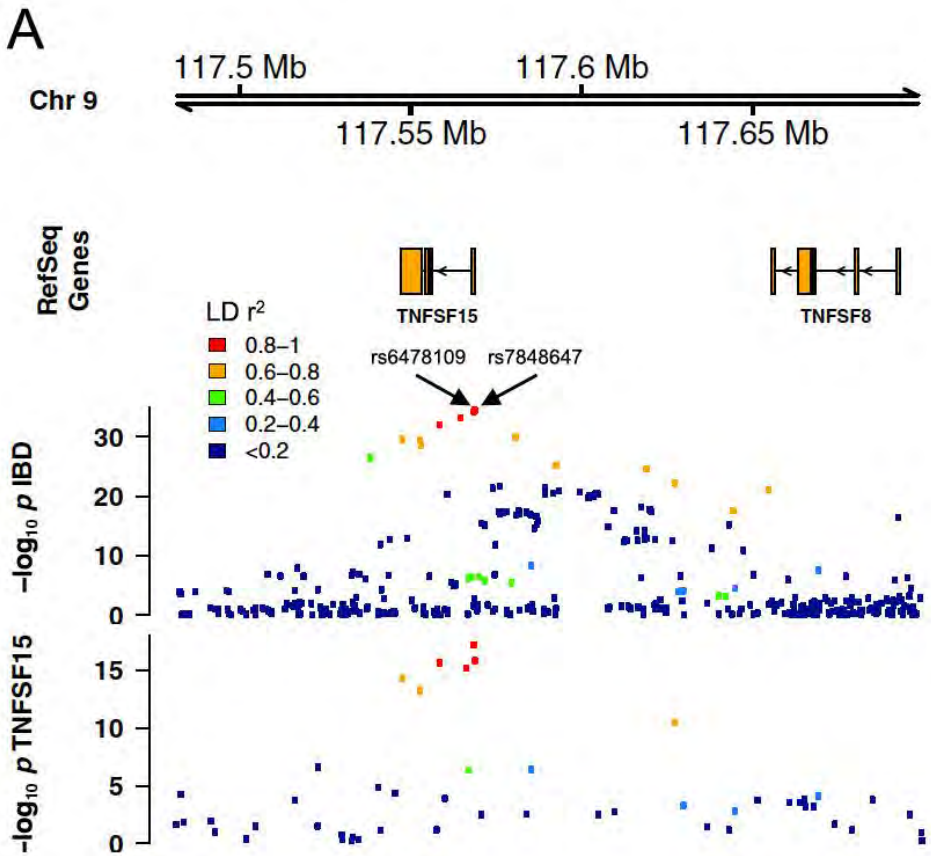
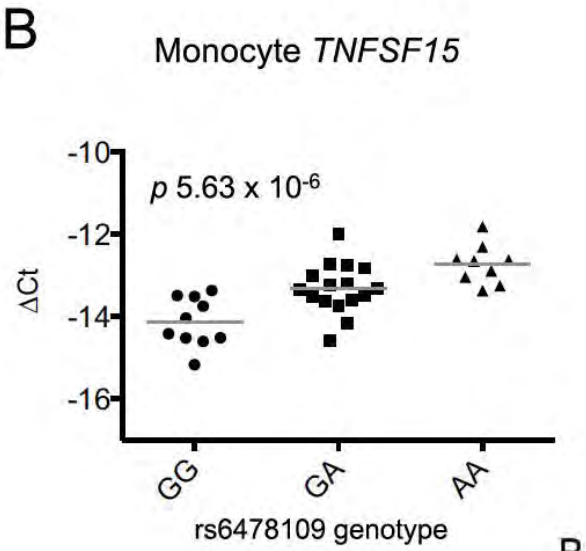
The example of anti-TL1A therapy



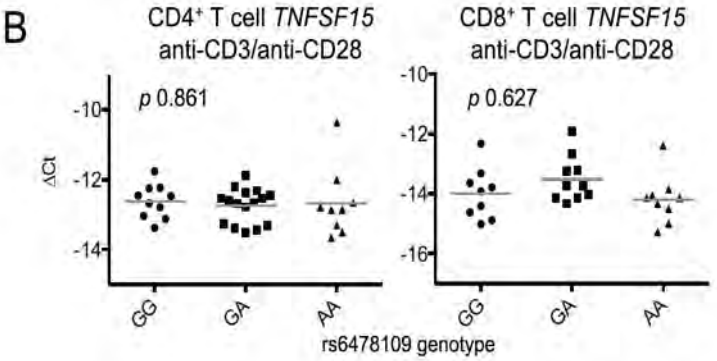




rs6478109

A (EUR minor allele) = IBD protective

G (EUR major allele) = IBD risk



In contrast to previous speculation that *TNFSF15* predisposes to inflammatory disease, this suggests a novel **protective role** for this cytokine in **preventing** the **development of human IBD**.

Ricard et al. Plos Genetics 2018.

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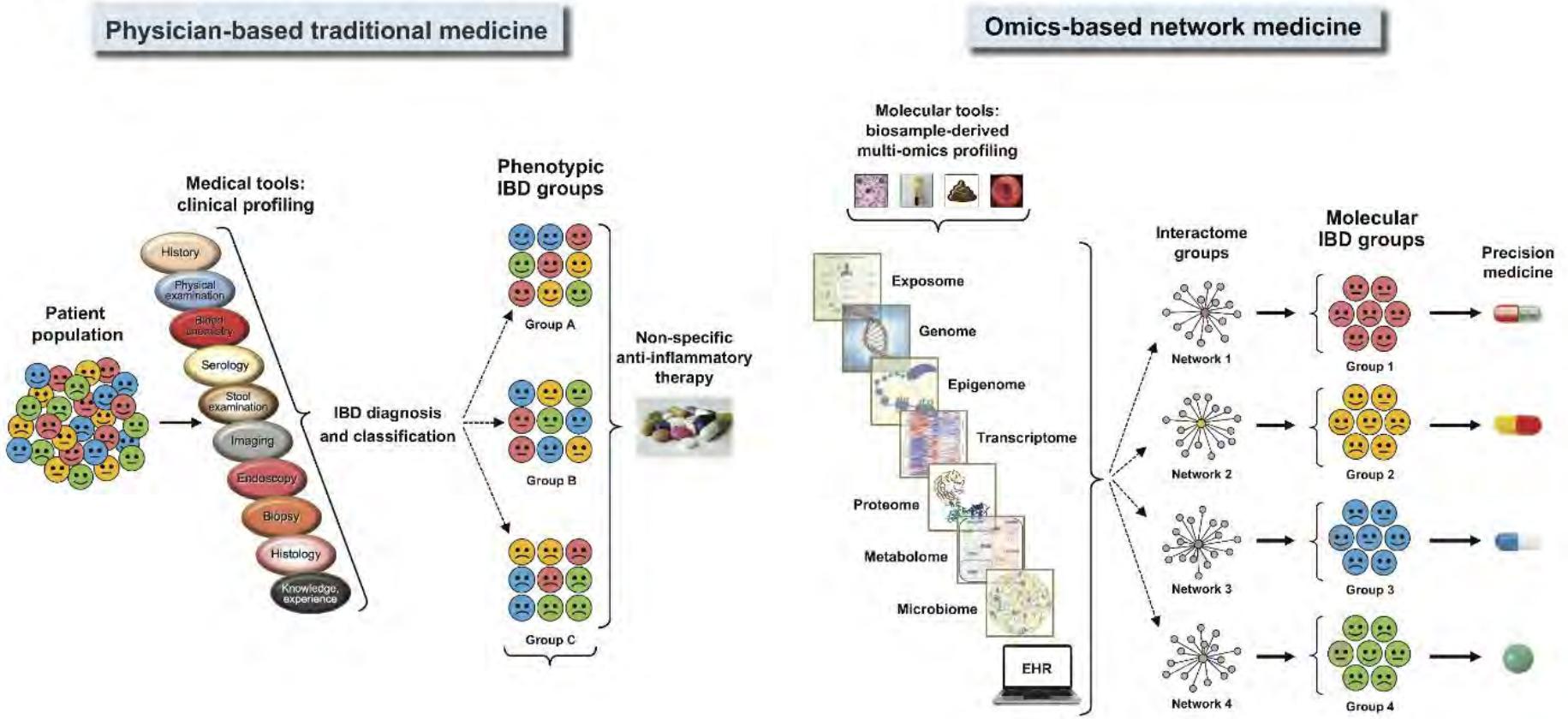
The path forward: reverting the process



Fiocchi et al. JCC 2022.

Conclusion

- **Precision medicine** is IBD key to **improve outcome** and **reduce disabilty** in our patients.
- We face **many obstacles** and have to **prioritise** some **key principles** to move the needle, with a focus to **start from the biology** in an **unsupervised** manner.
- We need to **work together**, academia and industry, to raise the bar, **VALIDATE** and make precision medicine a reality.
- **Anti-TL1A therapy** is the first drug development program with a **potential companion diagnostic**, although validation is mandatory in phase III.

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Leuven IBD group

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